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Well-Defined Palladium-(II) Complexes for Ligand-Enabled C(sp^3)-H Alkynylation†

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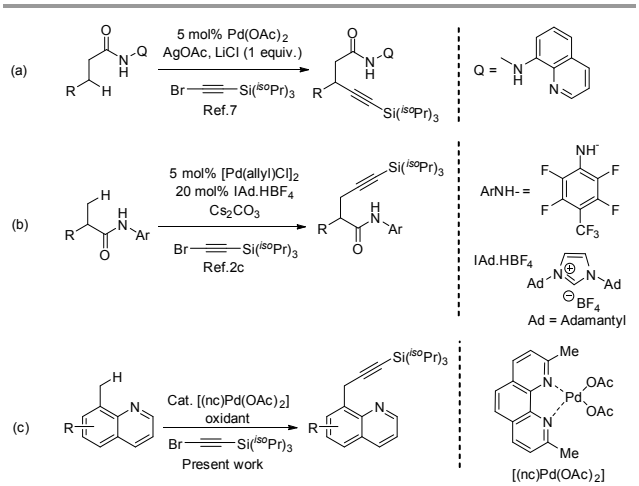
The first example of ligand-enabled C(sp^3)-H alkynylation of 8-methylquinoline is reported. The reaction is catalysed by the well-defined Pd(II)-complexes. The present C(sp^3)-alkynylation has a broad substrate scope as well as functional group tolerance and proceed efficiently under mild conditions.

Catalysts based direct activation of C-H bonds provides a sustainable and an atom-economical synthetic strategy to diverse organic molecules from simple, pre-functionalized substrates. The selection of ligands is very crucial in the design of such active catalytic systems. Ligands would alter the electronic and steric properties of the active catalyst and thus they could significantly accelerate C-H activation and successive bond forming reactions. Although, ligand-enabled C(sp^3)-H activation has emerged as a powerful tool for rapid, straightforward construction of the carbon-carbon and the carbon-heteroatom bonds, there still remains a significant challenge in the field of C(sp^3)-H activation.[1-2]

Development of the catalytic systems for direct conversion of inert C-H bonds into the C-alkynyl bonds is very attractive, simplest, and sustainable method as the alkyne moiety is of significant importance for various organic transformations including cycloaddition, metathesis, click reaction *etc.*[3] In addition, alkynes are excellent building blocks in synthetic chemistry and in material science and they are also a common motif in drugs.[4] Despite a number of reports concerning transition-metal catalysed C(sp^2)-H alkynylation reactions,[5-6] methods to convert C(sp^3)-H bonds to C(sp^3)-alkynyl bonds remain extremely rare.[2c,7] To date, there are only two reports describing the C-H alkynylation of inert C(sp^3)-H bonds. The first example was reported by Chatani and his co-workers by chelate assisted strategy using the pre-installed bi-dentate ligand under Pd(II)/Pd(IV) catalysis (Scheme 1a).[7] Another example of Pd(0)/*N*-heterocyclic carbene (NHC) and Pd(0)/PR_3-catalyzed alkynylation of β-C(sp^3)-H bonds using an *N*-arylamide auxiliary was reported by research group of Yu (Scheme 1b).[2c] In recent times, due to cyclometalation ability of 8-methylquinoline several transition-metal catalyzed C(sp^3)-H bond activation of 8-methylquinoline has been reported by various groups.[8-9] Very recently, a rhodium(III)-catalyzed C(sp^3)-alkenylation of 8-methylquinolines with internal alkynes has been reported.[8u] However, to the best of our knowledge, there is no report describing the C(sp^3)-alkynylation of 8-methylquinolines. Inspired by these studies, we were motivated to examine the possibility of C(sp^3)-H alkynylation of 8-methylquinoline **1a** using (triisopropylsilyl)ethynyl bromide **2** as an alkyne coupling partner. Herein, we report the first example of C(sp^3)-H alkynylation of 8-methylquinolines catalysed by well-defined palladium complexes (Scheme 1c). Notably, this reaction is enabled by neocuproine ligand to enhance the catalytic activity of active Pd(II) species. The present transformation has broad substrate scope, functional group tolerance and proceed efficiently under mild conditions.



Scheme 1. Direct conversion of inert C(sp^3)-H bonds into C(sp^3)-alkynyl bonds.

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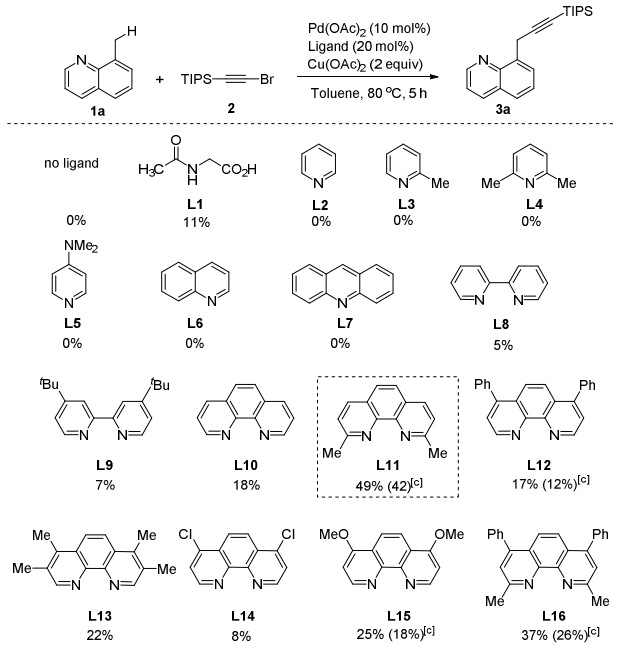
Initial experiments were performed with 8-methylquinoline (**1a**) and TIPS-alkynyl bromide (**2**) in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% Ac-Gly-OH (**L1**) as the catalytic system and 2 equiv. of $Cu(OAc)_2$ as an oxidant at 80 °C in toluene afforded the C(sp^3)-alkynylated product **3a** only in 11% yield. With the preliminary results in hand, we were interested to investigate a more appropriate ligand that can potentially improve the yield of the reaction. Yu and his co-workers observed that the pyridine- and quinoline-based ligands are good commodities for C(sp^3)-H activation.[2b,2d] Thus a tool-box of ligands were tested for the C(sp^3)-H alkynylation reaction of **1a**. Importantly, pyridine and quinoline-based ligands have no effects on alkynylation reaction and 1,10-phenanthroline-based ligands have improved this transformation (Table 1).

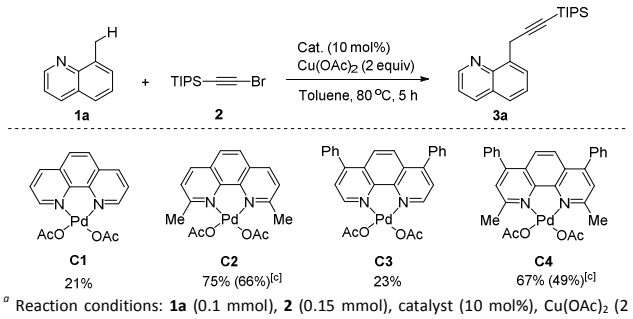
Table 1. Screening of ligands for C(sp^3)-alkynylation.[a,b]



[a] Reaction conditions: **1a** (0.1 mmol), (triisopropylsilyl)ethynyl bromide **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), $Cu(OAc)_2$ (2 equiv), toluene (1 mL), 80 °C, 5 h. [b] The yield was determined by ^{1}H NMR analysis of the crude product using dibromomethane as the internal standard. [c] Yield of isolated product.

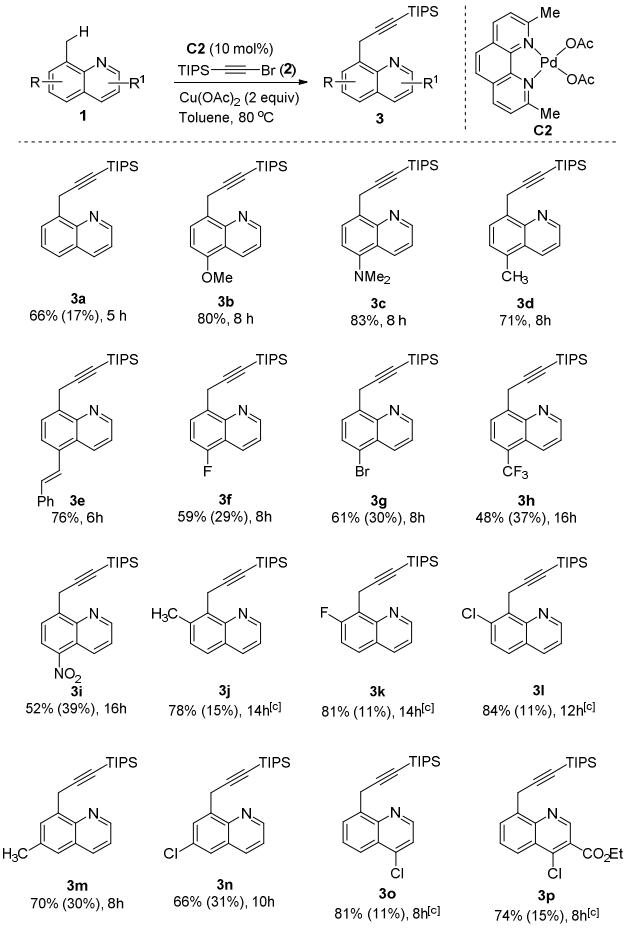
We have optimized the reaction conditions by performing extensive screening of Pd sources, mol% of catalyst, ligands, oxidants, solvent, temperature, and time to obtain the optimum yield of **3a** (see ESI). After extensive screening, toluene was found to be the optimal solvent as it suppressed the homocoupling of **2** and a combination of $Pd(OAc)_2$ and neocuproine (nc) **L11** were found to be more appropriate for this transformation and increased the yield (up to 49%) under standard conditions. It is important to note that, by using the pre-formed neocuproine palladium complex [(nc)$Pd(OAc)_2$] **C2**, the yield of **3a** was increased to 75% (Table 2). A well-defined bathocuproine derived Pd(II)-complex **C4** also showed comparable reactivity and yielded **3a** in 67%. However, the reaction did not proceed in the absence of $Cu(OAc)_2$.

Table 2. Screening of well-defined Pd(II)-complexes for C(sp^3)-alkynylation of **1a**.[a,b]



[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), catalyst (10 mol%), $Cu(OAc)_2$ (2 equiv), toluene (1 mL), 80 °C, 5 h. [b] The yield was determined by ^{1}H NMR analysis of the crude product using dibromomethane as the internal standard. [c] Yield of isolated product.

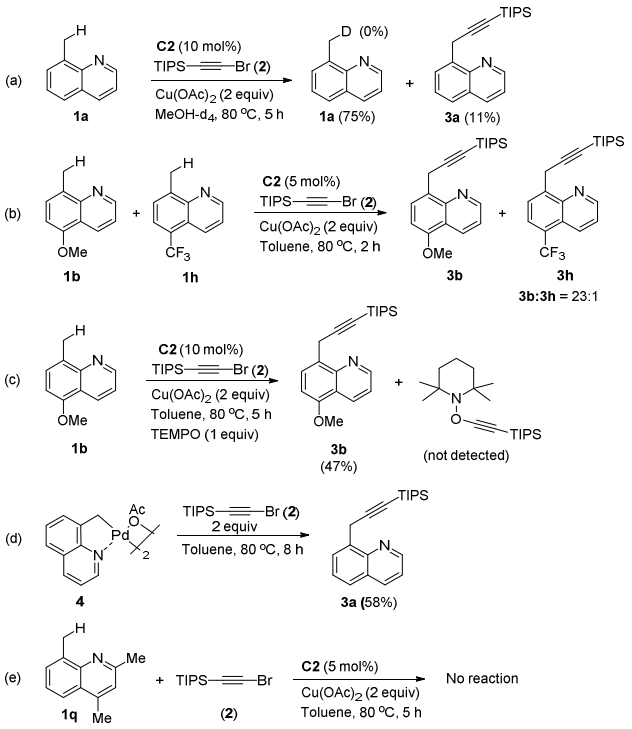
Table 3. Scope studies of C(sp^3)-alkynylation of **1**.[a,b]



[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), complex **C2** (10 mol%), $Cu(OAc)_2$ (2 equiv) and toluene (1 mL) in a 10 mL screw-capped viol were heated at 80 °C for specified time. [b] Yields of isolated products and yields in parentheses are based upon recovered starting material. [c] 25 mol% of complex **C2** was used.

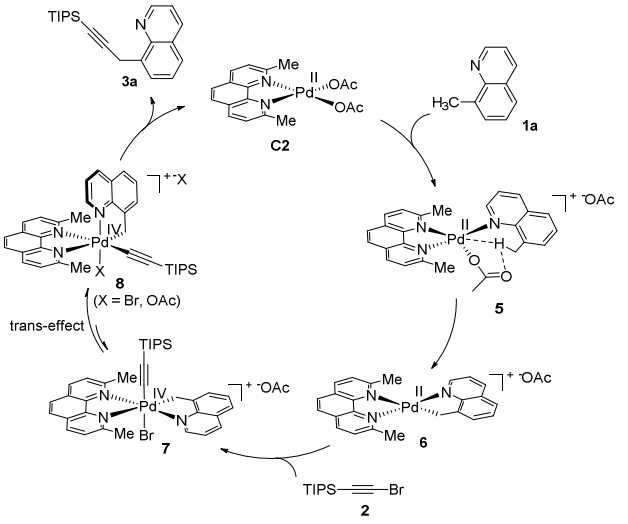
With the optimized reaction conditions in hand, we next explored the scope of the reaction. As shown in Table 3, C(sp^3)-H alkynylation proceeded at 80 °C in good to excellent

yields with a variety of electronically diverse substrates. In all cases, a well-defined palladium complex [(nc)Pd(OAc)$_2$] (10 mol%), and oxidant Cu(OAc)$_2$ (2 equiv) were used to achieve excellent yields. From the data in Table 3, we have observed the following trends in the C(sp^3)-H alkynylation reaction: i) Different substituents on the quinoline moiety were compatible with the alkynylation. Electron-donating groups proceeded smoothly to provide corresponding C(sp^3)-alkynylated products **3b**, **3c**, and **3e** in 80%, 83% and 76% isolated yields respectively, wherein electron-withdrawing groups were found to decrease the yields (48% of **3h** and 52% of **3i** respectively). ii) It is noteworthy that halide substituents were tolerated (**3f**-**3g**, **3k**-**3l**, and **3n**-**3p**), as this is advantageous for further synthetic elaborations with transition-metal catalysis thereby broadening the diversity of the products. iii) The position of the substituents on the quinoline moiety played a vital role and thus 5-substituted substrates worked slightly better than 6-substituted substrates. In case of 7-substituted 8-methylquinolines (**3j**-**3l**) higher yield of alkynylated product (78% of **3j**, 81% of **3k**, and 84% of **3l**) was obtained by using 25 mol% of catalyst. A multisubstituted ethyl 4-chloro-8-methylquinoline-3-carboxylate (**3p**) also gave desired alkynylated product. Notably, 2,4-dimethyl-8-methylquinoline (**1q**, Scheme 2e) showed no reaction probably due to steric reasons. In most cases, the unreacted starting materials were recovered.[10]



Scheme 2. Mechanistic studies on C(sp^3)-alkynylation reaction.

To shed some light on the mechanism of this ligand enabled C(sp^3)-alkynylation reaction, a series of control experiments, deuterium-labeling, radical trapping studies were performed.[11] When the reaction was carried out under standard condition in MeOH-d_4 at 80 °C for 5 hrs (Scheme 2a), no deuteration of the methyl C-H bonds was observed in the recovered **1a**, indicating that the C(sp^3)-H bond activation is irreversible, whereas it was found to be reversible in rhodium(III)-catalyzed alkenylation of 8-methylquinolines with alkynes.[8u] Competition experiment was used to determine the preference of the reaction for electronically different 8-methylquinoline compounds (Scheme 2b). When 5-methoxy-8-methylquinoline (**1b**) was used in competition with 8-methyl-5-(trifluoromethyl)quinoline (**1h**), the electron-donating group was preferentially alkynylated (**3b**/**3h**: ~23:1). These findings clearly confirmed that the acidity of the C(sp^3)-H bond being cleaved is trivial in the C-H activation and similar trend was observed in previously reported palladium-catalyzed *ortho*-alkynylation of aromatic C(sp^2)-H bonds.[6o] Additionally, we performed a radical trapping experiment to know whether a single electron transfer (SET) was involved in this reaction. Hence, performing the reaction in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under standard conditions, the reaction was not completely inhibited and no *O*-alkynylated-TEMPO product was detected, suggesting that the reaction does not involve SET mechanism. However, an alternative mechanism for Pd-catalyzed oxidative transformations involving binuclear Pd(III) species that does not involve free radicals is also possible.[13] Stoichiometric reaction of preformed palladacycle(II) of 8-methylquinoline (**4**) with 0.5 equiv of **2** in the absence of oxidant selectively yielded **3a** (58%), indicating that the Pd$^{II/IV}$ pathway may be operative for this alkynylation reaction.[14]



Scheme 3. A plausible mechanism for the C(sp^3)-alkynylation of **1a** with **2** catalyzed by **C2.**

Based on above experimental results and literature reports,[1c,12] we postulate that this Pd-catalyzed C(sp^3)-alkynylation reaction proceeds through a C-H palladation/coupling sequence and that a Pd$^{II/IV}$ manifold is operative and a plausible mechanism is shown in Scheme 3. As shown in Scheme 3, the coordination of the 8-methylquinoline **1a** to the Pd(II)-complex **C2** followed by a cyclopalladation lead to the intermediate **6**. The oxidative addition

of (triisopropylsilyl)ethynyl bromide **2**[14,15] lead to the formation of the hypervalent $Pd^{(IV)}$ intermediate **7.** The intermediate **7** may reassembled due to strong *trans-effect* of bi-dentate pyridyl ligand[16] (neocuproine) leading to **8** followed by a reductive elimination gives **3a** with the regeneration of the active $Pd^{(II)}$ species.

In conclusion, we have reported the fist example of ligand-enabled C(sp^3)-alkynylation of 8-methylquinolines with TIPS-alkynyl bromide. The reaction is catalyzed by the well-defined Pd(II)-complexes and proceed efficiently under mild conditions. The present C(sp^3)-C(sp) bond forming reaction has a broad substrate scope as well as functional group tolerance. Further studies to explore catalytic application of well-defined Pd(II)-complexes for other C-H activation reactions, and detailed mechanistic studies to understand significant role of ligand are under progress.

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14 The use of $Cu(OAc)_2$ as an oxidant is important and responsible for the Pd(II)-Pd(IV) oxidation since the TIPS-alkynyl bromide probably is not enough oxidising to do that (Scheme 3). Moreover, as suggested it also acts as an additive (e.g., a base responsible for binding HBr and as an acetate source) in the catalyst regeneration step. Thus, we can hardly believe that $Cu(OAc)_2$ acts as both an additive and an oxidant.

15 Other less hindered alkynyl halides (1-iodo-2-(trimethylsilyl)acetylene and (bromoethynyl)benzene) were not reactive, presumably a strong coordination of the alkyne moiety with the palladium center and thus may prevent the oxidative addition step (also see ref. 2c).

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Table of Contents (TOC)

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